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## **An update on the safety of psychostimulants for the treatment of attention-deficit/hyperactivity disorder**

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# An update on the safety of CNS stimulants for the treatment of ADHD

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## Abstract

Introduction: Methylphenidate is the first-line pharmacological treatment of attention-deficit/hyperactivity disorder (ADHD). Although methylphenidate has a well-established evidence base for treating ADHD, its long-term benefits are unclear.

Areas covered: Physical adverse effects, psychiatric adverse events and brain development

Expert opinion: Some physical adverse events have been described (e.g. sleep disturbances, growth reduction, loss of appetite), although most are of transient nature. Psychiatric adverse events seem more related to the diagnosis ADHD itself, and not stimulant treatment.

Concluding, short-to-mid-term use (i.e., up to 2 years) stimulants are relatively safe, but much less is known about longer-term efficacy and safety of these drugs.

Key words: ADHD, Stimulant treatment, methylphenidate, safety

## Contents

1. Introduction
2. Adverse physical events
  - 2.1. Growth
  - 2.2. Cardiovascular health
  - 2.3. Seizures
3. Adverse psychiatric events
  - 3.1. Tics
  - 3.2. Psychotic events
  - 3.3. Mood problems and suicidality
  - 3.4. Substance-related disorders
  - 3.5. Sleep problems
4. Effects on brain development
5. Drug- drug interactions
6. Expert opinion

## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate symptoms of inattention, hyperactivity, and impulsivity [1]. ADHD affects around 3 to 4% of children and adolescents [2] and often continues into adulthood [3] with rates in adulthood varying around 2.5% [4]. Stimulant medication such as methylphenidate and dexamphetamine form the first-line pharmacological treatment of ADHD [5]. Stimulants increase the synaptic availability of dopamine [6]. Although the short-term evidence base of stimulants is well-established [7, 8], its long term benefits are still unclear [9]. While serious adverse events are very rare, common adverse effects include sleep disturbances [10], loss of appetite and reduced growth [11]. Other concerns regarding stimulants include their possible effects on cardiovascular health and on brain development, and their risk of inducing other psychiatric problems.

While the majority of studies assessing the safety of methylphenidate have been performed in children or adolescents, dosing and adverse effects of methylphenidate in adults are very similar to those reported in pediatric samples: in an open-label flexible dose study of OROS methylphenidate for the treatment of adults with ADHD (N =370), adverse events were reported in 68% of patients and most were mild or moderate in severity; most frequently reported included headache (17%), decreased appetite (13%), and insomnia (11%) [12]. Small mean increases in systolic and diastolic blood pressure (both 2.4 mmHg) and pulse (3.2 bpm) were observed. Body weight decreased slightly (-1.5 kg). Medication was adjusted to optimize efficacy and tolerability for each patient. Furthermore, adverse events, vital signs, and laboratory parameters were assessed. The final dispensed doses were 18 mg (8%), 36 mg (29%), 54 mg (34%), 72 mg (20%), or 90 mg (9%). Thus there are no marked differences

between adult and pediatric samples concerning adverse events and dose.

In this narrative review we have summarized relevant and recent literature about adverse physical and psychiatric events following stimulant treatment in individuals with ADHD.

## 2. Adverse physical events

### 2.1. Growth.

Stimulant treatment has repeatedly been associated with reduced growth [11], potentially due to treatment-induced loss of appetite [13]. Alternatively, increases in synaptic dopamine may reduce the secretion of growth hormone, which in turn may lead to a reduction in growth [14]. However, a longitudinal study found no effect of stimulant treatment on growth hormone secretion [15].

Although effects on growth have generally been minor [16], large variability in those affected has been described [17]. Interestingly, in adulthood there is no difference in height between those who have or have not been treated with stimulants in their youth [18]. This observation has resulted in two mechanistic theories about the effects of stimulants on growth. The delayed growth theory states that, after initial slowing of growth in those treated with stimulants, growth rates return to normal with continued use. The second theory states that discontinuing use, for example during drug holidays, will lower the risk of growth deficits. As stated in the review by Faraone, there is evidence supporting both mechanisms. Taking drug holidays does not resolve the growth deficit [19], possibly because a six-week period is not sufficiently long to catch-up on a full year of growth. Thus, while many studies have been performed on this topic, at this moment no consensus exists on the exact mechanism

underlying stimulant-induced growth reduction. Trouble with these studies is that they were mostly done retrospectively or did not have a sufficiently long enough follow-up period, and did not use a detailed report of pharmacological history.

The European Guidelines Group advises adequate monitoring of children's weight and height using growth charts every six months during treatment. If concerns arise, a first focus should be on improving nutrition [16]. While drug holidays seem the obvious option, these should be applied with caution. Drug holidays can put a strain on families with ADHD because symptoms may reemerge and may temporarily worsen.

## 2.2. Cardiovascular health.

Stimulants have long been regarded as drugs with a low probability of serious cardiovascular events. Mild elevations of heart rate and blood pressure after stimulant administration have been well documented, resulting from the sympathomimetic effects of these drugs. Early on, this has prompted recommendations for appropriate monitoring of cardiovascular function in stimulant users and assessing the personal and familial history of cardiovascular diseases [20, 21]. In recent years, incidental reports of sudden cardiac death in treated children have fueled major concerns about the safety of stimulant treatment amongst professionals, policy makers, and the general public [22]. These concerns are strengthened by the increased prevalence and duration of stimulant use in children and adults with ADHD symptoms [23]. Indeed, many experts express their caution as the long-term effects of stimulant use (i.e., > two years) on cardiovascular health are not yet fully known, which might pose a particular threat in individuals at risk for cardiovascular disease or with a known condition [20, 21, 22, 24]. As a consequence, in recent years a growing number of meta-analytic and systematic reviews on

the role of stimulants for cardiovascular health have been published. Moreover, the number of high-quality studies including large population-based samples or randomized placebo-controlled clinical trials is mounting. Obviously, low sample sizes are a threat for underestimating risk of serious events of stimulant users, given their low prevalence in the general population.

Mazza and colleagues [25] conducted a meta-analysis of three large observational studies in mostly young individuals with ADHD currently using stimulants for more than one year. The authors reported no increased risk of sudden cardiac death or stroke in this group. Their meta-analysis included 806,162 person-years (498,556–1,663,560), showing rates of 10.5/100,000 person-years (4.4–16.5) of sudden death and 14.13/100,000 person-years (5.88–22.37) of stroke. At least ten large population-based studies in both children and adolescents as well as adults are now available [e.g., reviewed in 22, 26] with over > 5,000,000 observed patient-years [27]. These studies are mostly based on retrospective reports [28, 29, 30] derived from various sources, such as U.S. state and federal death registries and databases of U.S. insurance claims or UK general practitioners. Reviews have concluded that sudden death or other serious adverse events (e.g., myocardial infarction, stroke, ventricular arrhythmia, all-cause mortality) are extremely rare amongst stimulant users and do not appear to occur beyond the risk of non-users in the general population [20, 21, 22, 31, 32, 33]. Studies with a mean duration of 2.1 years of follow-up in children and adolescents and a mean duration of 0.33 years of current use in adults [21, 29] pointed to encouraging safety with respect to the short- and medium-term use of stimulants.

Another available meta-analysis based on ten adult controlled trials reported an increased resting heart rate [+5.7bpm (3.6,7.8)] and systolic blood pressure [+2.0mmHg (0.8,3.2)]

associated with stimulant use in adults [24]. These subtle elevations (heart rate  $\leq 10$  bpm, blood pressure  $\leq 5$  mmHg), which are not considered clinically relevant, are in line with the more extensive child literature on stimulant use in ADHD [20, 31]. Also, to date, there is no evidence for deviations in electrocardiographic parameters such as prolonged QTc interval [20, 24, 31].

Critical notes have been expressed as well, pointing to methodological issues (e.g., insufficient control of confounding, selection bias, incomplete medical records, unknown influence of time and dose effects) and still underpowered studies in both child and adult populations [21, 26]. These issues may have contributed to false negative findings, although methodological flaws have also been pointed out in studies reporting increased cardiovascular risks [34, 35, 36], as discussed by various authors [20, 22, 26, 27, 37]. Although Schelleman [30] found an 1.8-fold increased risk of sudden death or ventricular arrhythmia in stimulant users versus non-users, the authors concluded that there was no causal link between stimulant use and cardiovascular risk, given that dose was inversely related to this risk.

To conclude, current evidence on the cardiovascular safety of stimulant use in children, adolescents, and adults with ADHD symptoms is encouraging for the short- and medium-term use (< two years), with an extremely low risk of serious cardiovascular events. Several important challenges need to be addressed in future research. Studies of long-term exposure to stimulants (> two years) are rare and therefore highly needed [38], which will require very large, sufficiently powered population-based databases, and will have to overcome methodological criticisms [26]. In particular, there is a need to assess the potential long-term effects of the stimulant-induced increase in heart rate and blood pressure, taking into account that cardiovascular function varies with age. The sympathetic effects of stimulants may



possibly predispose certain users to serious cardiovascular problems on the longer term or lead to pathological changes over time [20, 25]. For example, the Multimodal Treatment Study of Children with ADHD (MTA) found increased heart rate at 10-year follow-up [see 21, 39]. Moreover, risk-assessment in vulnerable individuals is needed, for example in those with (pre)hypertension, metabolic syndrome, or other cardiovascular conditions [32], as well as in those with a familial history of cardiovascular disease. Studies in these areas are still sparse and current research has often selected on healthy ADHD subjects without known pre-existing cardiovascular problems. Finally, more attention should be drawn to stimulant use in adults, as adults are still underrepresented in the current literature, yet are more likely to show signs of cardiovascular wear and tear due to aging. Before we can rule out long-term cardiovascular risks of stimulant use in vulnerable and non-vulnerable subjects, more high quality, long-term research needs to be conducted, for example, by using data from nationwide birth cohorts and joining forces across large prospective population-based studies around the globe.

### 2.3. Seizures.

While the summary of product characteristics states that methylphenidate should be used with caution in patients with epilepsy and that it may lower the convulsive threshold in patients with a prior history of seizures, this warning is not actually justified by research findings. A recent systematic review identified seven prospective studies and two retrospective studies, and none of these studies reported higher seizure rates after exposure to methylphenidate [40]. Moreover, methylphenidate is also effective for the treatment of ADHD symptoms in patients with epilepsy [41, 42].

### 3. Psychiatric outcomes

#### 3.1. Tics.

The presence of a tic disorder and even a family history of tic disorders is a contraindication for the use of methylphenidate according to the United States Food and Drug Administration. This warning reflects worries that methylphenidate may evoke tics in susceptible individuals (i.e., those with a family history) and may exacerbate tics in those with existing tics.

However, these contraindications stem from anecdotal reports but are not backed by a recent meta-analysis [43]. One of the first case reports describing a possible link of methylphenidate treatment with the subsequent development of tics appeared over 40 years ago [44]. A nine-year-old boy then described as having clinically typical ‘minimal brain dysfunction’ developed Tourette syndrome eight weeks after the start of therapy with methylphenidate with tics persisting after methylphenidate was discontinued. More case reports described the onset of tics after the initiation of methylphenidate therapy [45, 46, 47] along with case reports in which exacerbation of tics after the use of methylphenidate in children with pre-existing Tourette syndrome were described [48]. However, in a large case series involving 1520 children, tics developed in only 14 children and became worse in only six children with pre-existing tics after methylphenidate administration [49]. Subsequent authors challenged the causal link between methylphenidate and the provocation or exacerbation of tics and concluded that there is virtually no evidence that stimulants may cause or exacerbate tics [50]. This was confirmed in small controlled studies investigating the effects of varying doses of methylphenidate in children with a tic disorder, with none of the doses leading to an increase in tics [51, 52, 53]. Others, though, continued to note that methylphenidate may increase the severity of tics in a portion of patients with Tourette syndrome [44, 54, 55]. However, a

blinded placebo-controlled cross-over study reported relatively high rates of tic onsets or exacerbations, but no differences between the placebo and methylphenidate condition were seen [56]. Another placebo-controlled study confirmed that the proportion of individual subjects with Tourette syndrome reporting a worsening of tics was no higher in those treated with methylphenidate than those being administered placebo [57]. Pooled data from three placebo-controlled studies also showed that the incidence of tics was not significantly different across those treated with osmotic-controlled release oral delivery system (OROS) methylphenidate, short acting methylphenidate, or placebo [58]. Finally, a recent meta-analysis of 22 controlled trials involving 2,385 children [43] seems to have settled the issue its results did not support an association between new onset or worsening of tics and use of psychostimulants, with these events being similarly reported in the stimulant (event rate = 5.7%, 95% CI = 3.7%-8.6%) and placebo groups (event rate = 6.5%, 95% CI = 4.4%-9.5%). In conclusion, despite the official Food and Drug Administration's contraindication and despite the official Food and Drug administration's contraindication and despite previous concerns in the literature methylphenidate does not appear to pose a risk for the development or exacerbation of tics. When such events do occur in a child, these symptoms are much more likely to be coincidental rather than caused by methylphenidate.

### 3.2. Psychotic events.

As methylphenidate enhances the synaptic availability of dopamine it might be expected to pose a risk factor for psychotic episodes. Indeed, a number of case studies have described the onset of psychotic features in children prescribed methylphenidate [59, 60, 61]. Moreover, in a high-risk cohort of children of whom one or both parents were affected with major depressive disorder, bipolar disorder, or schizophrenia, 62.5% of those who had taken

stimulants had psychotic symptoms, compared with 27.4% in those who had never taken stimulants. Moreover, in cases that were assessed both on and off stimulants, there was an association between current stimulant use and concurrent psychotic symptoms, supporting a temporal relationship between use of stimulants and psychotic symptoms [62]. Furthermore, in a cohort of individuals who had developed psychotic disorders, the age of onset of psychosis was significantly lower in those previously exposed to stimulants [20.5 vs. 24.6 years stimulants vs. no stimulants; 63]. In another large-scale cohort study of individuals who were newly diagnosed with ADHD, methylphenidate use significantly increased the risk of developing any psychotic disorder except schizophrenia [64]. There have been no trials investigating psychopharmacological treatment of patients with schizophrenia and ADHD. These observations suggest a relationship between methylphenidate treatment and the onset of psychotic events. In contrast, a well-designed, large-scale study, involving 20,586 individuals did not support this, but indicated an increased risk of psychotic events before but not during prescription of methylphenidate. This points to an association of psychotic events with ADHD symptoms rather than with methylphenidate [65]. Thus it is likely that previous study results suggesting a link between methylphenidate use and psychotic events may be partially explained by ADHD being a risk factor for the later development of psychotic disorders [66], and that the link between methylphenidate and psychotic events may be limited to transient psychosis in susceptible individuals.

### 3.3. Mood problems and suicidality

While individuals with ADHD have an increased risk of developing a depressive or bipolar disorder, longer treatment with methylphenidate has actually been demonstrated to protect against these disorders [67, 68]. However, bipolar disorder and ADHD show a high degree of

symptom overlap and comorbidity. Clinical trials and case reports indicate that psychostimulants do not or only rarely trigger or aggravate manic episodes and can even produce rapid and pronounced antimanic effects [69]. Other studies have also pointed out that methylphenidate may improve mood problems [70]. Moreover, a large-scale registry based longitudinal study found no evidence for a positive association between the use of methylphenidate and the risk of concomitant suicidal behavior among individuals with ADHD. If anything, the results pointed to a potential protective effect of methylphenidate on suicidal behavior [71].

A common worry, however, of parents is that treatment with methylphenidate may lead to dampening of spontaneity and/or a flat affect. So far, perceived adverse events of methylphenidate on cognition (such as reasoning, depth/breadth of thinking, intellectual capacity, and creativity), motivation (e.g., drive, effort, and attitudes toward rewards/incentives) and mood (e.g., dampening of spontaneity/flat affect, mood dysregulation, increased anxiety/edginess) have not been systematically assessed. A recent study used a qualitative semi-structured interview to capture such adverse events of methylphenidate. This has led to the development of a new questionnaire that can be used for monitoring such events in medication trials or routine clinical care [72]. This new instrument is certainly very welcome given the scarcity of data in this area.

### 3.4. Substance-related disorders.

Individuals with ADHD are at increased risk of developing substance-related disorders and nicotine dependence [73]. Despite great research investments, the mechanisms underlying this increased risk remain unclear. Worries have been voiced that treating ADHD with stimulants

increases the risk of developing substance-related disorders later in life and that treatment with stimulants may aggravate substance misuse in those individuals with co-occurring substance-related disorders and ADHD.

Seeing that stimulants have the potential to be addictive, professionals and parents have been concerned that stimulant treatment may have a negative effect on the development of substance use disorders (SUDs) in ADHD [74]. These concerns are mainly based on the sensitization hypothesis, stating that exposure to stimulants may increase substance abuse by increasing the sensitivity to the reinforcing effects of previously experienced drugs (i.e., stimulant treatment). This, in turn, may result in a higher risk of developing substance-related disorders and nicotine dependence. Only one study in humans has found an increased risk of smoking and cocaine use in those previously treated with stimulants, but possibly results of these studies were confounded by higher comorbidities in the stimulant group [75]. Two well-performed recent meta-analyses of prospective studies have further invalidated these concerns. While one meta-analysis reported a protective effect of stimulant treatment on the development of tobacco use [76], the other found that stimulant treatment did not affect the development of substance use disorder or nicotine dependence [77]. These inconsistent results may be due to differences in outcome measure severity (i.e. tobacco use vs. nicotine dependence), but also due to unknown underlying moderators. Factors that might enhance the protective effects of stimulant treatment on substance-related disorders include an earlier onset of stimulant use [78, 79] and longer duration of stimulant use [79, 80]. Note that other studies did not replicate these findings [e.g., 81]. However, the evidence for a protective effect of characteristics of stimulant use is scarce, and the interaction between these factors has not been described. Interestingly, one study found an increased risk of substance-related disorders in those individuals with who had only used *nonstimulant* medication [79].

Summarizing, the evidence suggests that treating ADHD in childhood with stimulants does not increase the risk of developing substance-related disorders later in life, but further research into the mechanisms of a possible protective effect of stimulants on the later development is warranted.

Among those suffering from substance-related disorders, the prevalence of ADHD is high [23.1%;82]. Treatment in these individuals already suffering from substance-related disorders is an area of concern. The main concern is misuse of stimulant medication. Immediate release stimulants have a higher potential of misuse than long acting stimulants [83]. The most common methods of misuse of immediate release stimulants are intranasal (“snorting”) or injection of crushed tablets [84]. The second area of concern is the efficacy of ADHD treatment. Little research has been performed on the efficacy in of pharmacological interventions for co-occurring ADHD and substance-related disorders. The studies that have been done, show an improvement in ADHD symptoms, but not substance-related disorders [85]. According to the self-medication theory, individuals with ADHD use drugs of abuse to reduce their ADHD symptoms. Following this reasoning, one can assume that a reduction in ADHD symptoms (due to pharmacological treatment) would lead to a reduction in substance-related behaviors. However, no evidence for this has been found [85]. Furthermore, the use of stimulants in combination with alcohol or drugs only mildly increases the number of side effects experienced [86]. Guidelines typically advice abstinence before commencing pharmacological treatment of ADHD, prescription of drugs with lower misuse potential (e.g. atomoxetine, or long-acting stimulants), and/or close monitoring by a trained professional [5]. In sum, stimulant treatment of co-occurring ADHD and substance-related disorders is effective in treating symptoms of ADHD, but not substance use severity. However, due to the

misuse potential of short acting formulations, caution should be taken in prescribing these formulations.

Stimulant treatment of ADHD early in life does not seem to impose a risk for the later development of substance-related disorders. Certain characteristics of medication use (e.g. longer duration of use, younger onset age) may induce a protective effect on the later development of substance use problems, but more research is warranted to elucidate these complex issues. Regarding pharmacological treatment of adolescents and adults with co-occurring ADHD and substance-related disorders, caution is warranted. Concerns are mainly based on misuse potential and side effects.

### 3.5.Sleep.

A 60% increase in the number of sleep disturbances is reported after the use of stimulant treatment [13]. This can have a great impact on quality of life [87]. Complicating this relationship are findings that medication naive children with ADHD experience sleep problems as well [88], but also findings that show sleep problems can aggravate symptoms of ADHD and comorbid disorders [89], and even suggestions that sleep problems are at the base of ADHD [90]. Despite these complexities, it is likely that sleep disturbances are already present in children with ADHD, and that stimulant treatment can aggravate these problems. A recent meta-analysis showed that stimulant medication leads to a longer sleep latency, worse sleep efficiency, and shorter sleep duration [91]. Dose effects have been found on sleep latency and sleep duration [92]. Frequency of the dose also moderated sleep latency [91], although this could reflect the effect of immediate release versus extended release formulas. Overall, there are indications that sleep disturbances can emerge due to stimulant treatment.



Moreover, it has been suggested that there is a genetic vulnerability (i.e. carriers of 10/10 DAT1 genotype) to somatic adverse events, such as sleep disturbances. However, more research is warranted to elucidate working mechanisms concerning this important issue. The European guidelines group recommends that sleep analyses is done before initiating stimulant treatment. If sleep problems persist or intensify after stimulant treatment, one may consider switching to non-stimulant medication [16] or a long-acting stimulant with a shorter duration. Behavioral interventions have been shown efficacious in treating insomnia in children with ADHD [93].

#### 4. Brain development

##### 4.1. Structural and functional magnetic resonance imaging

Concerns that stimulant treatment may adversely affect brain development are frequently voiced. Evidence for stimulant-induced damage to dopaminergic nerve terminals stems almost exclusively from animal studies, in which stimulants are typically administered in binge-like patterns at high dosages. To investigate the effects of stimulant treatment in humans, most researchers resort to magnetic resonance imaging (MRI) that provides indirect measurements of brain structure and function.

Several structural MRI studies have suggested that long-term stimulant treatment may result in normalization of brain structure, although findings have been mixed. Two meta-analyses reported indirect evidence that stimulant treatment is associated with more normative basal ganglia volumes: across studies, findings of caudate nucleus and putamen volume reduction were more pronounced when predominantly medication-naïve individuals were included, as

compared to when more previously treated individuals were included [94, 95]. However, large-scale studies failed to detect volumetric differences in the striatum between treated and untreated patients, or associations between treatment duration and striatal volumes [96, 97, 98, 99, 100, 101]. In other brain regions, including the lateral prefrontal cortex, anterior cingulate cortex, thalamus, and cerebellum, treatment effects suggestive of normalization have been reported [98, 102, 103, 104]. Here, treatment-naïve children with ADHD, but not those with a history of stimulant treatment, showed significant volume reductions compared to their typically developing peers. In a unique large-scale longitudinal study, Shaw et al. [99] found that over time, non-medicated adolescents with ADHD showed excessive cortical thinning compared to typically developing adolescents, whereas those who received stimulant medication did not. Again, other equally sized studies have reported null-findings i.e. no association between stimulant treatment and cortical thickness [105]. Summarizing, the literature on long-term stimulant treatment effects on brain structure is mixed, with several studies suggesting normalization, other reporting no brain changes after treatment, but no studies reporting detrimental effects. Future investigations may benefit from studying individual differences between patients, as illustrated by our study in which we found normalization of frontal cortex volume after stimulant treatment, but only in young carriers of the *DRD4* 7R-allele [101].

Functional MRI (fMRI) studies have almost exclusively focused on the immediate rather than long-term effects of methylphenidate. In such studies, patients typically undergo scanning twice (once with and once without medication) while performing a cognitive task. A fairly consistent picture of acute stimulant effects emerges across various experimental designs. During cognitive control tasks, methylphenidate was found to normalize brain activation patterns by enhancing activation in fronto-striatal circuits [106, 107, 108, 109]. During tasks

tapping into attention, methylphenidate appeared to at least partially normalize brain activation and functional connectivity patterns in children with ADHD [110, 111] while at the same time eliciting non-normalizing, compensatory activation in the prefrontal cortex that was not evident in typically developing children [110]. Studies investigating acute stimulant effects during working memory tasks have yielded inconsistent results; whereas some suggested increased activity in frontal networks [112, 113], others reported reduced or unchanged frontal cortex activation patterns after methylphenidate administration [114, 115]. Finally, two resting-state fMRI studies suggested that methylphenidate might have an acute normalizing effect on striatal and cerebellar activation during rest [116, 117]. In sum, there is compelling evidence that a single dose of methylphenidate attenuates aberrant brain activation and functional connectivity patterns in children with ADHD, during tasks of cognitive control and attention as well as during rest.

In contrast, potential long-term changes in brain function after stimulant treatment have received very little attention. To study lasting changes in brain activation patterns, patients with diverse treatment histories should be scanned while off medication. In a pharmacological MRI study, Schrantz et al. [118] found that after a one week wash-out period, children with ADHD who had received four months of stimulant treatment showed increased cerebral blood flow in response to a dopamine challenge, as compared to children who had received placebo. Conventional fMRI studies into long-term effects of treatment have all used cognitive tasks. During cognitive control, no difference was found in overall brain activation patterns between children who had received long-term treatment and those who had not, suggesting no lasting effect of treatment after wash-out [119, 120]. By contrast, brain activation patterns during reward processing were found to be associated with stimulant treatment history. Individuals with ADHD show reduced activation of the striatum in response to reward [121]. No such

reduction was found in adult patients with a history of childhood stimulant treatment [122]. A second study, however, found no evidence of normalized striatal activation patterns, but did find compensatory recruitment of the dorsal anterior cingulate cortex and supplementary motor area [123]. We conclude that there may be changes in brain activation patterns after childhood stimulant treatment that last after wash-out, but more studies are needed to confirm this.

## 5. Drug- drug interactions

Methylphenidate should not be used in patients being treated (currently or within the proceeding 2 weeks) with monoamine oxidase inhibitors. Because of possible increases in blood pressure, it should be used cautiously with vasopressor agents. Also, methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors) [124]. Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate.

## 6. Expert opinion

Stimulants such as methylphenidate are frequently being prescribed to children and adolescents because of ADHD. The short-term effects of methylphenidate in reducing the core ADHD symptom domains of hyperactivity, impulsivity, and inattention are well established. However, the same cannot be said about its long-term benefits, i.e., beyond a treatment duration of two years. For obvious ethical issues, high quality RCTs cannot be

performed to examine long-term effects of treatment. Evidence that is available at this point on long-term efficacy is derived from observational longitudinal studies, and come with its pitfalls. Also, the benefits of the drug on relevant functional outcomes such as academic achievement and the quality of peer relationships are less clear. Another concern is the growing use of stimulant treatment in ADHD. Most guidelines state that methylphenidate may only be considered as first line treatment in the case of severe ADHD, while in mild-to-moderate ADHD the first line treatment should be behavioral interventions such as parent training. We doubt that such a severity distinction is routinely done in clinical practice, or that it is difficult for clinicians to make such distinctions. The subjective boundaries of a diagnosis of ADHD, forms a related problem in light of the growing use of stimulants in treating ADHD.

With regard to the short-to-mid-term use (i.e., up to 2 years) stimulants are relatively safe. There appears to be no increased risk of cardiovascular death. However, mild adverse events do occur frequently; most notably decreased appetite and sleep disturbance, which can severely decrease quality of life, and should be monitored frequently. Recent meta-analyses indicate no risk of inducing or exacerbating tics, seizures, psychotic symptoms, substance misuse, or mood problems through stimulants. Well-conducted studies indicate that it is far more likely that ADHD in itself is associated with such symptoms rather than stimulant medication. Also, there is no indication of detrimental effects of stimulants on brain development. The safety situation on the longer term is much less well studied. This is a concern given that treatment duration of up to five years or longer is quite common in clinical practice, but hardly any high quality studies have been performed on this topic. Future studies should be aimed at longer-term outcomes, but also make use of higher detailed medication records instead of a mere yes/no variable. Especially the long-term cardiovascular safety

deserves better studies. A relatively unexplored area of research is that of sexual dysfunction following stimulant use. So far mainly case reports have been written on this topic [125] as initial reports are worrying, and larger scale studies are warranted in this area. A final important area for future studies would be to more systematically assess adverse effects of stimulants on cognition, motivation, and dampening of spontaneity/flat affect, mood dysregulation, and increased anxiety/edginess.

Summarizing, some physical adverse events have been described (e.g. sleep disturbances, growth reduction, loss of appetite), although most are of transient nature. Psychiatric adverse events seem more related to the diagnosis ADHD itself, and not stimulant treatment. Concluding, short-to-mid-term use (i.e., up to 2 years) of stimulants is relatively safe, but much less is known about longer-term efficacy and safety of these drugs.

## Highlights

- Mild adverse events occur frequently, most notably decreased appetite and sleep disturbance.
- Adverse events can severely decrease quality of life, and should be monitored frequently.
- Psychiatric adverse events, such as exacerbating tics, seizures, psychotic symptoms, substance misuse, or mood problems, seem primarily related to the diagnosis of ADHD itself, and not stimulant treatment.
- Short-to-mid-term use (i.e., up to 2 years) of stimulants is relatively safe, but much less is known about longer-term efficacy and safety of these drugs, and longitudinal prospective studies are necessary.

- More research is warranted on adverse effects of stimulants on cognition, motivation, and dampening of spontaneity/flat affect, mood dysregulation, and increased anxiety/edginess.

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